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ORIGINAL ARTICLE

Antibiotic therapy for *Enterococcus* bacteraemia: warning for the antimicrobial stewardship team

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Abstract

Enterococci are a significant cause of bacteraemia in healthcare-associated infections (HCAI), being resistant to cephalosporins and aminoglycosides often used in this setting. Our aim was to measure the rate of inefficient antimicrobial therapy and its impact on the outcome. We conducted a retrospective multicentre cohort study in 6 French institutions. Patients were identified through the laboratory's database, which extracted all positive blood cultures for *Enterococcus* spp. in 2016. Patients' data were gathered by reviewing hospital records. Efficient antimicrobial therapy was defined as any therapy containing at least one antibiotic compound with in vitro efficacy against *Enterococcus* spp.: amoxicillin, amoxicillin/clavulanic acid, piperacillin, piperacillin/tazobactam, imipenem, meropenem, vancomycin, daptomycin, linezolide, tigecycline. A short-term unfavourable outcome was defined as intensive care requirement and/or in-hospital death at least 48 h after positive blood culture. One hundred thirty-one patients were included; the main diagnosis was a urinary tract infection (46%) and a HCAI was observed in 54% of the cases. Four patients did not receive any antibiotic. Forty-three per cent of empirical antibiotic therapies and 17% of documented ones were inefficient for enterococcal bacteraemia. Sixty patients (46%) received amoxicillin as a documented therapy. Twenty-three per cent of the patients presented a short-term unfavourable outcome. Univariate and multivariate analyses showed that not receiving amoxicillin as a documented antibiotic therapy was associated with an unfavourable short-term outcome ($p = 0.001$). In conclusion, Enterococcal bacteraemia was associated with a high proportion of inefficient antimicrobial therapy. In multivariate analysis, amoxicillin use was associated with a better outcome.

Keywords *Enterococcus* · Bacteraemia · Antibiotic therapy · Outcome · Audit

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Introduction

Enterococcus spp. are ubiquitous bacteria, as part of the intestinal microbiota, and may colonize the urinary tract. The most common species are *E. faecalis* and *E. faecium*. A rising incidence of invasive enterococcus infection has been reported since the past decades [1–3]. In France, the proportion of *E. faecalis* isolated from healthcare-associated infections (HCAI) is higher in 2017 than in 2012 (6.5% versus 4.6% respectively), being now the third pathogen after *Escherichia coli* and *Staphylococcus aureus* [4]. Accordingly, *Enterococcus* spp. are a significant cause of bacteraemia in the healthcare setting, accounting for 14% of all cases, and appear to be an opportunistic pathogen [5, 6].

The major sources of enterococcal invasive infections are the urinary and digestive tracts [7–9]. Enterococcal bacteraemias are also observed in patients exposed to invasive

devices such as central venous line. Thus, depending on study designs, enterococcal bacteraemia are considered to be an HCAI in 7 to 23% of all cases [10]. Furthermore, between 8 and 25% of patients with enterococcal bacteraemia develop an infective endocarditis [1, 11, 12]. These data imply that enterococcal bacteraemias are associated with a high rate of unfavourable outcome, the rate of death being measured over 20% [1, 8, 9].

The antimicrobial treatment of enterococcal invasive infections has to take into account the natural resistance of the bacteria to cephalosporins, and an increasing prevalence of acquired resistance to penicillins and aminoglycosides is observed [3, 10]. *E. faecalis*, the main species isolated in human medicine remains most of the time susceptible to amoxicillin [7, 8]. *E. faecium* bacteraemias are associated with a higher mortality than *E. faecalis* ones, probably related to a lower efficacy of penicillins and subsequent inappropriate empirical antibiotic therapy [8, 9, 13].

The unfavourable outcome of enterococcal bacteraemia is probably caused by several factors, such as the burden of comorbidities and the inappropriate and/or delayed efficient therapy [14–16]. Moreover, another study also showed that vancomycin-susceptible *E. faecium* bacteraemias were associated with higher in-hospital mortality and prolonged length of stay than *E. faecalis* bacteraemias [17]. To the best of our knowledge, no published study has described the antibiotic therapy for enterococcal bacteraemia in real life, with an "antimicrobial stewardship approach", evaluating the quality of the empirical therapy as well as its reassessment. Our aim was to describe such approach and to determine the risk factors associated with a favourable outcome.

Methods

Study setting and design

We conducted a retrospective multicentre cohort study of patients with enterococcal bacteraemia in several institutions in France working in a multidisciplinary professional network. The participating institutions worked together to develop antibiotic stewardship programme through common audits and clinical researches [18–20].

The French National Health Agency promotes antibiotic audits and patients, or relatives gave their written consent for computerizing their personal data for hospitalization purpose and potential clinical research.

Population

Patients were identified through the laboratory's electronic database, which extracted all positive blood cultures for *Enterococcus* spp. between 1 January 2016 and 31 December 2016. We included all patients with at least one positive blood culture for *Enterococcus* spp. and for whom full records were available. Patients with multiple blood cultures positive for the same *Enterococcus* during the same hospitalization were included only once. Patients with polymicrobial blood cultures, including *Enterococcus* spp., were excluded, as we wanted to determine the quality of the antibiotic treatment against enterococcal infections.

Clinical characteristics

Only patients 18 years old or older were included. Patients' data were gathered by reviewing hospital electronic records, and, when incomplete, by reviewing stored hard copy medical records. We reported the following: demographic data, comorbidities, immunosuppressive treatment, reasons for hospital admission, surgical procedures and invasive device exposure, source of bacteraemia as defined by the doctor in charge, creatinine value at the closest measurement to bacteraemia date, intensive care unit requirement and/or dialysis, hospital stay duration and final outcome. Data regarding antimicrobial treatments included antibiotic choice and treatment duration.

We used the definition proposed by Friedman et al. in 2002 for healthcare-associated bloodstream infection [21, 22]. Thus, the bacteraemia was considered as HCAI when diagnosed $\geq$ 48 h after hospital admission or for patients with regular hospital visits (haemodialysis, chemotherapy in the 30 days before the bloodstream infection), patients receiving intravenous therapy at home or wound care, within 90 days after two or more days of hospitalization, or for patients residing in a nursing home on a long-term care facility.

An enterococcal bacteraemia diagnosed within 48 h of hospital admission was considered to be community acquired.

Microbiological characteristics

The microbiological data included the following: enterococcal species causing bacteraemia, antibiotic susceptibility results and other relevant culture results within 30 days of the first positive blood culture.

Blood cultures were collected directly during the venepuncture procedure using aerobic (Bact/AERT® FA Plus, Biomérieux, France) and anaerobic (Bact/AERT® FN Plus, Biomérieux, France) blood culture bottles. Blood cultures were sent to the laboratory and processed with an automated Bactalert 3D system (BioMérieux, France). The date of the positivity of the blood culture was the date the blood culture was sampled.

Antimicrobial therapies

Empirical antimicrobial therapy was defined by those antibiotic(s) prescribed in front of a septic patient and/

or those linked to the first notification of Gram positive read on blood culture.

Documented antimicrobial therapy was defined as the antibiotic(s) prescribed after the definitive bacterial identification and determination of drug susceptibility.

Efficient antimicrobial therapy was defined as any therapy containing at least one antibiotic compound efficient against *Enterococcus* spp.: amoxicillin, amoxicillin/clavulanic acid, piperacillin, piperacillin/tazobactam, imipenem, meropenem, vancomycin, daptomycin, linezolide, tigecycline, combined or not with gentamicin.

Inappropriate antimicrobial therapy was defined by any other antibiotic compounds, including cotrimoxazole or fluoroquinolones, combined or not with gentamicin.

Dosage and duration of treatment were not included in the definition of "appropriate" antimicrobial therapy, as it may be a source of disagreement between physicians and/or ID specialists.

Outcome

Primary outcome was the clinical consequence of the antibiotic treatment. We were interested in short-term unfavourable outcome defined by an intensive care requirement and/or in-hospital death after positive blood culture, during hospitalization. As a secondary analysis, we also evaluated the outcome at day 7 after positive blood culture. As long-time follow-up was insufficient for most of the patients, we decided therefore not to study long-term outcome.

Statistical analyses

First, we performed descriptive analysis, using absolute values and proportions for qualitative variables, and mean (with standard error) or median (with interquartile range (IQR)) for quantitative variables. Then, we performed a univariate analysis, comparing variables with a Chi-square test, or a Fisher test, and a Student *t* test, or a Wilcoxon–Mann–Whitney test where needed. Finally, we performed a multivariate analysis. All variables with a p value < 0.2 in univariate analysis were entered into the model.

Results

Population

The centres were two public general hospitals, one teaching hospital and 3 private institutions. The private institutions were clinics with 283, 198 and 225 beds. They had both medical and surgical wards and they all had an Emergency Department and an Intensive Care Unit. Four institutions had a dialysis centre.

A total of 131 patients presented monomicrobial enterococcal bacteraemia during the 1-year study period. Their main clinical characteristics are detailed in Table 1. The most frequent portal of entry for bacteraemia was the urinary tract (60/131; 46%), the digestive tract (21/131; 16%) and intravascular catheter (18/131; 14%). For 25/131 patients (19%), the portal of entry was unknown. Infection was a HCAI in 71 cases (54%), notably related to urologic surgery ($n = 16$; 23%).

One hundred ten infections (84%) were caused by *E. faecalis* and 13 cases (10%) were caused by *E. faecium*. Nine infections (7%) were due to other *Enterococcus* spp.: *E. durans* (5/9) and *E. dispar*, *E. avium*, *E. gallinarum* and *E. hirae* (1/9 cases each).

In vitro susceptibility indicated that 7/131 strains (5%) were amoxicillin resistant (*E. faecium* strains exclusively), none was vancomycin resistant and 26/131 strains (20%) were gentamicin resistant (high level of resistance).

Empirical antimicrobial therapy

Twenty patients (15%) did not receive any antimicrobial therapy before the microbiological identification.

Among the 111 patients who received an empirical antimicrobial therapy, 45/111 (41%) benefited of a single antibiotic using 10 different options, 55/111 (50%) received simultaneously two antibiotics with 19 different options and the other 11/111 patients (10%) received simultaneously three antibiotics using 10 different options (see Table 2). According to definitions, an efficient empirical antibiotic therapy was prescribed in 63/131 (48%) cases.

Documented antimicrobial therapy

Four patients (4/131; 3%) did not receive any antimicrobial therapy after the availability of bacterial identification and determination of drug susceptibility. Also, despite the latter, for nine other patients, no antibiotic reassessment was reported.

Among the 118 patients who received a documented antimicrobial therapy, 84/118 (71%) received a single antibiotic using 11 different drugs, 32/118 (27%) received simultaneously two antibiotics using 15 different drugs and 2/118 (2%) patients received simultaneously three antibiotics (see Table 2). Out of 118, 98 (83%) patients received an efficient therapy; the efficient antimicrobial therapy was amoxicillin in 60/98 (61%) cases. In contrast, 20/118 (17%) patients did not benefit from an active antibiotic against *Enterococcus* spp.

Patient outcome

Among the 131 patients, 30/131 (23%) presented a short-term unfavourable outcome defined by an admission to intensive

Table 1 Main patients' characteristics

	$n = 131$ (%)	Favourable outcome, $n = 91$	Unfavourable outcome, $n = 30$	p value
Establishment				
Teaching hospital	49 (37.4)	37 (40.7)	12 (40.0)	0.987
General hospitals	21 (16.0)	16 (17.6)	5 (16.7)	
Clinics	61 (46.6)	38 (41.8)	13 (43.3)	
Sex ratio (M/F)	3.4	3.0	5.0	0.456
Age* (median [IQR])	76 [69–84]	76 [69–84]	80 [73–85]	0.128
Length of stay[§] (median [IQR])	17 [12–36]	17 [11.25–34.50]	22 [13.75–40.25]	0.515
Delay between admission and first blood culture positivity[§] (median [IQR])	3 [0–16]	1 [0–8]	14 [1.5–18.75]	0.025
Charlson (median [IQR])	3 [1–4]	2 [1–4]	3 [2–5]	0.309
Cardiovascular comorbidity	94 (71.8)	63 (69.2)	26 (86.7)	0.052
Pulmonary comorbidity	21 (16.0)	12 (13.2)	8 (26.7)	0.092
Chronic kidney failure	38 (29.0)	26 (28.6)	11 (36.7)	0.494
Gastroenterologic comorbidity	34 (26.0)	24 (26.4)	8 (26.7)	1
Neurologic comorbidity	22 (16.8)	19 (20.9)	3 (10.0)	0.306
Cancer	51 (38.9)	33 (36.3)	12 (40.0)	0.814
Diabetes mellitus	24 (18.3)	17 (18.7)	6 (20.0)	1
Immunosuppressive treatment	25 (19.1)	20 (22)	5 (17)	0.794
Portal of entry				
Urinary	60 (45.8)	45 (49.5)	11 (36.7)	0.314
Digestive	21 (16.0)	13 (14.3)	4 (13.3)	1
Intravascular catheter	18 (13.7)	10 (11.0)	6 (20.0)	0.222
Unknown	25 (19.0)	18 (19.8)	7 (23.3)	0.875
Endocarditis	4 (3.1)	3 (3.3)	1 (3.3)	–
Orthopaedic	3 (2.3)	2 (2.2)	1 (3.3)	–
Amoxicillin resistance				
Yes	7 (5.3)	88	26	0.063
No	114 (87.0)	3	4	
Amoxicillin treatment				
Empirical treatment	8	6	2	1
Documented treatment	59[#]	50	6	**0.001**
Documented antimicrobial therapy appropriate	63 (48)	53/84 (63.1)	10/24 (41.7)	0.100

*Years old

[§] Days

[#] Three missing data concerning the outcome of patients receiving amoxicillin as a documented treatment

care and/or death. The median of hospitalization lengths of stay was 12 days IQR [5.5–18].

In univariate analysis, we found that an appropriate documented antimicrobial therapy was associated with a trend towards a better short-term outcome: $p = 0.100$ (see Table 1). Also, in univariate and multivariate analyses, the prescription of documented antimicrobial therapy that contains amoxicillin was significantly associated with a favourable short-term outcome: $p < 0.001$ (see Table 3). With a 7-day cut-off as definition of unfavourable outcome, documented antimicrobial therapy that contains amoxicillin was still significantly associated with a favourable short-term outcome: $p = 0.016$ (see Table 4).

Discussion

The antimicrobial stewardship programme aims to reduce misuse (and overuse) of antibiotic therapy to fight against the emergence of multidrug-resistant bacteria [23]. Focusing on enterococcal bacteraemia, we found that a huge diversity of antibiotic therapies was prescribed for these septic patients. Moreover, 50% and 17% of the patients did not benefit from an efficient empirical antimicrobial and efficient documented therapy respectively. Finally, we found that using amoxicillin during enterococcal bacteraemia was associated with a better short-term outcome ($p < 0.001$).

Table 2 Antibiotic therapy for enterococcal bacteraemia

Empirical antimicrobial therapy	*n* = 111	Documented antimicrobial therapy	*n* = 118
One antibiotic	***n* = 45**	**One antibiotic**	***n* = 84**
3GC	11	AMX	44
Piperacillin/tazobactam	8	AMX/clavulanate acid	13
AMX/clavulanate acid	7	Piperacillin/tazobactam	7
Carbapenem	6	FQ	8
Amoxicillin	4	IV 3GC	3
Fluoroquinolone	4	Oral 3GC	2
Vancomycine	2	Vancomycin	2
Fosfomycine-trometamol	1	Carbapenem	3
Cotrimoxazole	1	Linezolide	1
Cefazoline	1	Daptomycine	1
Two or three antibiotics	***n* = 66**	**Two or three antibiotics**	***n* = 34**
3GC + aminoglycoside	13	AMX + aminoglycoside	7
3GC + FQ	8	AMX + FQ	4
AMX/clavulanate acid + aminoglycoside	4	IV 3GC + FQ	4
AMX/clavulanate acid + fluoroquinolone	4	AMX/clavulanate acid + FQ	3
Piperacillin/tazobactam + aminoglycoside	3	AMX + rifampicin	2
Piperacillin/tazobactam + FQ	3	Vancomycin + aminoglycoside	2
FQ + aminoglycoside	3	3GC + metronidazole	2
3GC + metronidazole	3	AMX + IV 3GC	1
Vancomycin + aminoglycoside	2	AMX + cefazoline	1
AMX + aminoglycoside	2	Piperacillin/tazobactam + FQ	1
Imipenem + aminoglycoside	2	Piperacillin/tazobactam + linezolide	1
AMX/clavulanate acid + IV 3GC	1	Piperacillin/tazobactam + aminoglycoside	1
Cotrimoxazole + aminoglycoside	1	Vancomycin + metronidazole	1
AMX + cefazoline	1	FQ + cycline	1
AMX/clavulanate acid + vancomycin	1	Daptomycine + aminoglycoside	1
Piperacillin/tazobactam + linezolide	1	AMX + daptomycine + aminoglycoside	1
3GC + vancomycin	1	AMX/clavulanate acid + FQ + metronidazole	1
3GC + daptomycine	1		
Linezolide + aztreonam	1		
AMX/clavulanate acid +3GC + aminoglycoside	2		
AMX/clavulanate acid + metronidazole + aminoglycoside	1		
AMX/clavulanate acid + vancomycin + aminoglycoside	1		
AMX + daptomycine + aminoglycoside	1		
3GC + FQ + aminoglycoside	1		
3GC + metronidazole + aminoglycoside	1		
Piperacillin/tazobactam + linezolide + aminoglycoside	1		
Piperacillin/tazobactam + aminoglycoside + vancomycin	1		
Imipenem + vancomycin + linezolide	1		
Vancomycin + aminoglycoside + rifampicine	1		
Inefficient empirical therapy	**48 (43%)**	**Inefficient documented therapy**	**20 (17%)**

AMX, amoxicillin; *FQ*, fluoroquinolone;*3GC*, third-generation cephalosporins; *IV*, intra veinous

Our study has several limitations. This is a retrospective study and we faced some missing data, notably in the public teaching hospital in which the electronic patient records did not provide a date for the laboratory results, therefore limiting our effort to determine the reasons for treatment modifications. Also, antibiotic therapy durations were recorded for inpatient only. Lastly, we included all the patients with at least one positive blood culture. As suggested in the literature,

Table 3 Multivariate analysis for variables associated with the short-term outcome during hospitalization

	cOR [95%IC]	*p* value	aOR [95%IC]	*p* value
Establishment				
Teaching hospital	1.04 [0.31–3.43]	0.951	–	–
General hospitals	REFERENCE		–	
Clinics	1.09 [0.33–3.58]	0.881	–	
Sex ratio (M/F)	1.69 [0.58–4.93]	0.456	–	
Age*	1.03 [0.99–1.07]	0.146	1.03 [0.98–1.08]	0.291
Length of stay[§]	1.00 [0.99–1.02]	0.566	–	–
Delay between admission and first blood culture positivity[§]	1.00 [0.99–1.02]	0.669	1.00 [0.98–1.01]	0.857
Charlson (median [IQR])	1.08 [0.92–1.27]	0.347	–	–
Cardiovascular comorbidity	3.85 [1.08–13.79]	0.038	10.92 [1.12–105.71]	0.039
Pulmonary comorbidity	2.44 [0.88–6.75]	0.085	3.41 [0.78–14.87]	0.103
Chronic kidney failure	1.50 [0.63–3.62]	0.362	–	–
Gastroenterologic comorbidity	1.05 [0.41–2.68]	0.923	–	–
Neurologic comorbidity	0.43 [0.12–1.58]	0.204	–	–
Cancer	1.22 [0.52–2.87]	0.649	–	–
Diabetes mellitus	1.14 [0.40–3.22]	0.811	–	–
Immunosuppressive treatment				
Yes	0.74 [0.25–2.19]	0.585	–	–
No	REFERENCE		–	
Portal of entry				
Urinary	0.54 [0.22–1.32]	0.176	–	–
Digestive	0.68 [0.19–2.43]	0.549	–	–
Intravascular catheter	REFERENCE	–	–	–
Unknown			–	–
Endocarditis			–	–
Orthopaedic			–	–
Amoxicillin resistance				
Yes	0.22 [0.05–1.05]	0.058	0.65 [0.08–5.10]	0.680
No	REFERENCE		REFERENCE	
Amoxicillin treatment				
Empirical treatment	1.01 [0.19–5.30]	0.989	–	–
Documented treatment	**0.2 [0.07–0.54]**	**0.001**	**0.11 [0.02–0.46]**	**0.003**

95%IC, 95% confidence interval; *aOR*, adjusted odds ratio; *cOR*, crude odds ratio

*Years old

§ Days

Enterococcus species may be a contaminant in 10–15% of blood cultures [24, 25]. Accordingly, co-isolation with a skin organism suggests a contamination rather than a real blood stream infection [26].

Our study population was similar to previous reports concerning the rate of enterococcal bacteraemia observed in healthcare settings [4–6]. Of note, none of the isolates was vancomycin resistant in our study cohort. In 2017, in France, the percentage for vancomycin resistance in *E. faecium* was 0.8% while it was 14.9% in the European Union [27]. Indeed, the microbiological epidemiology is significantly different between countries, with national percentages of vancomycin resistance in 2017 ranging from 0 to 43.9% [27]. In contrast, American works report 82% and 9% of vancomycin-resistant *E. faecium* and *E. faecalis* strains respectively [28, 29].

Very few studies have focused on antimicrobial treatment of enterococcal bacteraemia. The diversity of antibiotics used for patients with bacteraemia has been already reported, suggesting that local or national guidelines are not respected in clinical practice [13, 16, 19]. Our data and other previous studies show that repeated audits with feedback information to clinicians are still major tools in antimicrobial stewardship programme.

In our work, nearly 50% of patients received an efficient empirical antimicrobial therapy, which is much more than

Table 4 Multivariate analysis for variables associated with the short-term outcome at day 7

	cOR [95%IC]	*p* value	aOR [95%IC]	*p* value
Establishment				
Teaching hospital	2.17 [0.55–8.59]	0.271	–	–
General hospitals	REFERENCE		–	
Clinics	0.44 [0.09–2.14]	0.306	–	
Sex ratio (M/F)	0.59 [0.20–1.71]	0.331	–	
Age*	1.00 [0.96–1.04]	0.994	–	–
Length of stay[§]	1.00 [0.99–1.02]	0.464		
Delay between admission and first blood culture positivity[§]	1.00 [0.99–1.02]	0.798	–	–
Charlson (median [IQR])	0.97 [0.79–1.20]	0.805	–	–
Cardiovascular comorbidity	3.69 [0.81–16.89]	0.092	2.09 [0.38–11.65]	0.399
Pulmonary comorbidity	1.41 [0.42–4.78]	0.579	–	–
Chronic kidney failure	1.15 [0.40–3.29]	0.799		
Gastroenterologic comorbidity	2.41 [0.88–6.66]	0.089	2.43 [0.71–8.30]	0.156
Neurologic comorbidity	0.23 [0.03–1.82]	0.164	0.17 [0.01–1.56]	0.118
Cancer	0.65 [0.23–1.83]	0.411	–	–
Diabetes mellitus	2.50 [0.83–7.48]	0.102	4.18 [1.10–15.86]	0.035
Immunosuppressive treatment				
Yes	0.19 [0.02–1.48]	0.112	0.17 [0.02–1.61]	0.121
No	REFERENCE		REFERENCE	
Portal of entry				
Urinary	0.39 [0.13–1.15]	0.088	0.57 [0.16–2.01]	0.379
Digestive	0.58 [0.14–2.32]	0.438	0.38 [0.07–1.92]	0.242
Intravascular catheter	REFERENCE	–		
Unknown			REFERENCE	–
Endocarditis				
Orthopaedic				
Amoxicillin resistance				
Yes	0.22 [0.04–1.05]	0.058	0.34 [0.04–3.08]	0.336
No	REFERENCE		REFERENCE	
Amoxicillin treatment				
Empirical treatment	1.91 [0.37–10.20]	0.450	–	–
Documented treatment	**0.24 [0.08–0.77]**	**0.016**	0.17 [0.04–0.70]	0.013

95%IC, 95% confidence interval; *aOR*, adjusted odds ratio; *cOR*, crude odds ratio

*Years old

[§] Days

elsewhere: it was 18% in Pinholt's study [1], but our efficient treatment list was broader than in the latter, considering imipenem and meropenem as efficient against *Enterococcus* spp. Antimicrobial reassessment enhanced amoxicillin use (from 6 to 46%), and decreased the use of carbapenem (from 9 to 3 patients), vancomycin (from 9 to 5 patients), third-generation cephalosporin (from 41 to 12 patients) and aminoglycosides (from 38 to 10 patients). However, the rate of patients who benefited from amoxicillin (46%) as a documented antimicrobial therapy remains insufficient. We do not have any explanation for this low level of use of this reference therapy recommended for susceptible enterococcal species, its bactericidal effect being sufficient to treat this infection [10]; it is also the cornerstone of enterococcal endocarditis [30]. Physicians might have been scared to treat bacteraemia with a narrow-spectrum antibiotic on frail patients. Yet, in our experience, the traceability of the information about the positivity of the blood culture is often transmitted by the physician from the Department of Clinical Microbiology to the nurse and not to the physician in charge of the patient. Therefore, as we cannot assert that the physicians had seen the bacteriological results, our results suggest that microbiological information was not fully used or even seen.

Lastly, the mortality rate was 15%, which is similar to other studies that worked on vancomycin-susceptible enterococcal bacteraemia (from 13 to 31%) [8, 31]. McBride et al. found

that an inefficient empirical antibiotic therapy against the enterococcal isolate was not associated with increased mortality, probably due to the low virulence of *Enterococcus* spp. [8]. In contrast, all other studies showed that inefficient documented antimicrobial therapy was associated with a higher mortality [8, 13, 32, 33].

Conclusion

A high level of inappropriate antimicrobial therapy, for both empirical and documented therapies, was observed during enterococcal bacteraemia. Among efficient antibiotics, amoxicillin use was associated with a better outcome. Since *Enterococcus* spp. are increasingly recognized as a causative agent of HCAI, the antimicrobial stewardship team should include enterococcal infections in their targets.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval Antibiotic audit is being promoted by French National Health Agency. As no personal data were extracted or copied from the computerized chart, patient privacy was protected.

Informed consent Patients or relatives give their written consent for computerizing their personal data for hospitalization purpose and potential clinical researches.

References

1. Pinholt M, Ostergaard C, Arpi M et al (2014) Incidence, clinical characteristics and 30-day mortality of enterococcal bacteraemia in Denmark 2006–2009: a population-based cohort study. Clin Microbiol Infect 20:145–145
2. DANMAP 2009 (2010) Use of antimicrobial agents and occurrence of antimicrobial resistance in bacteria from food animals, foods and humans in Denmark.. Available at: www.danmap.org. Accessed January 2019
3. Lester CH, Sandvang D, Olsen SS et al (2008) Emergence of ampicillin-resistant *Enterococcus faecium* in Danish hospitals. J Antimicrob Chemother 62:1203–1206
4. Enquête Nationale de Prévalence des Infections Nosocomiales et des Traitements Anti Infectieux en Etablissements de Santé, France mai – juin (2017) http://invs.santepubliquefrance.fr/Publications-et-outils/Rapports-et-syntheses/Maladies-infectieuses/2018/Enquete-nationale-de-prevalence-des-infections-nosocomiales-et-des-traitements-anti-infectieux-en-etablissements-de-sante-France-mai-juin-2017. Accessed January 2019
5. de Kraker ME, Jarlier V, Monen JC, Heuer OE, van de Sande N, Grundmann H (2013) The changing epidemiology of bacteraemias in Europe: trends from the European Antimicrobial Resistance Surveillance System. Clin Microbiol Infect 19:860–868
6. Coulter S, Roberts JA, Hajkowicz K, Halton K (2017) The use of bloodstream infection mortality to measure the impact of antimicrobial stewardship interventions: assessing the evidence. Infect Dis Rep 9:6849
7. Gray J, Marsh PJ, Stewart D, Pedler SJ (1994) Enterococcal bacteraemia: a prospective study of 125 episodes. J Hosp Infect 27:179–186
8. McBride SJ, Upton A, Roberts SA (2010) Clinical characteristics and outcomes of patients with vancomycin-susceptible *Enterococcus faecalis* and *Enterococcus faecium* bacteraemia—a five-year retrospective review. Eur J Clin Microbiol Infect Dis 29:107–114
9. Billington EO, Phang SH, Gregson DB et al (2014) Incidence, risk factors, and outcomes for *Enterococcus* spp. blood stream infections: a population-based study. Int J Infect Dis 26:76–82
10. Murray BE (1990) The life and times of the *Enterococcus*. Clin Microbiol Rev 3:46–65
11. Fernández-Guerrero ML, Herrero L, Bellver M, Gadea I, Roblas RF, de Górgolas M (2002) Nosocomial enterococcal endocarditis: a serious hazard for hospitalized patients with enterococcal bacteremia. J Intern Med 252:510–515
12. Anderson D, Murdoch DR, Sexton DJ et al (2004) Risk factors for infective endocarditis in patients with enterococcal bacteremia: a case-control study. Infection. 32:72–77
13. Suppli M, Aabenhus R, Harboe ZB, Andersen LP, Tvede M, Jensen JU (2011) Mortality in enterococcal bloodstream infections increases with inappropriate antimicrobial therapy. Clin Microbiol Infect 17:1078–1083
14. Cheah AL, Spelman T, Liew D et al (2013) Enterococcal bacteraemia: factors influencing mortality, length of stay and costs of hospitalization. Clin Microbiol Infect 19:E181–E189
15. Chang-Hua C, Li-Chen L, Yu-Jun C, Chih-Yen C (2016) Mortality analysis of *Enterococcus faecium* bloodstream infection in Central Taiwan. Rev Chilena Infect 33(4):395–402
16. Zasowski EJ, Claeys KC, Lagnf AM, Davis SL, Rybak MJ (2016) Time is of the essence: the impact of delayed antibiotic therapy on patient outcomes in hospital-onset enterococcal bloodstream infections. Clin Infect Dis 62
17. Kramer TS, Remschmidt C, Werner S et al (2018) The importance of adjusting for enterococcus species when assessing the burden of vancomycin resistance: a cohort study including over 1000 cases of enterococcal bloodstream infections. Antimicrob Resist Infect Control 7:133
18. Etienne P, Roger PM, Brofferio P et al (2011) Antimicrobial stewardship program and quality of antibiotic prescriptions. Med Mal Infect 41:608–612
19. Roger PM, Tabutin J, Blanc V et al (2015) Prosthetic joint infection: a pluridisciplinary multi-center audit bridging quality of care and outcome. Med Mal Infect 45:229–236
20. Aillet C, Jammes D, Fribourg A et al (2018) Bacteraemia in emergency departments: effective antibiotic reassessment is associated with a better outcome. Eur J Clin Microbiol Infect Dis 37:325–331
21. Friedman ND, Kaye KS, Stout JE et al (2002) Health care–associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. Ann Intern Med 137:791–797
22. Cardoso T, Almeida M, Friedman ND, Aragão I, Costa-Pereira A, Sarmento AE et al (2014) Classification of healthcare-associated infection: a systematic review 10 years after the first proposal. BMC Med 12:40. https://doi.org/10.1186/1741-7015-12-40
23. Dellit TH, Owens RC, McGowan JE Jr et al (2007) Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. Clin Infect Dis 44:159–177
24. Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G et al (1997) The clinical significance of positive blood cultures in the 1990s: a prospective comprehensive evaluation of

the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults. Clin Infect Dis 24:584–602
25. Pien BC, Sundaram P, Raoof N, Costa SF, Mirrett S, Woods CW et al (2010) The clinical and prognostic importance of positive blood cultures in adults. Am J Med 123:819–828
26. Freeman JT, Chen LF, Sexton DJ, Anderson DJ (2011) Blood culture contamination with enterococci and skin organisms: implications for surveillance definitions of primary bloodstream infections. Am J Infect Control 39:436–438
27. Surveillance of antimicrobial resistance in Europe 2017 (2018) European Centre for Disease Prevention and Control. http://ecdc.europa.eu/en/publications-data/surveillance-antimicrobial-resistance-europe-2017. Accessed January 2019
28. Rosenthal VD, Al-Abdely HM, El-Kholy AA et al (2016) International nosocomial infection control consortium report, data summary of 50 countries for 2010-2015: device-associated module. Am J Infect Control 44:1495–1504
29. Sievert DM, Ricks P, Edwards JR et al (2013) Antimicrobial-resistant pathogens associated with healthcare-associated infections: summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009-2010. Infect Control Hosp Epidemiol 34:1–4
30. Habib G, Lancellotti P, Antunes MJ et al (2015) Guidelines for the management of infective endocarditis. Eur Heart J 36:3075–3128
31. Poh CH, Oh HM, Tan AL (2006) Epidemiology and clinical outcome of enterococcal bacteraemia in an acute care hospital. J Inf Secur 52:383–386
32. Vergis EN, Hayden MK, Chow JW et al (2001) Determinants of vancomycin resistance and mortality rates in enterococcal bacteremia: a prospective multicenter study. Ann Intern Med 135:484–492
33. Caballero-Granado FJ, Becerril B, Cuberos L, Bernabeu M, Cisneros JM, Pachón J (2001) Attributable mortality rate and duration of hospital stay associated with enterococcal bacteremia. Clin Infect Dis 32:587–594